Non-motor Parkinson disease: new concepts and personalised management

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Summary

- Most patients with Parkinson disease (PD) have non-motor symptoms (NMS), and on average these can range from four to 19 different symptoms.
- NMS dominate the prodromal phase of PD and some may serve as clinical biomarkers of PD.
- NMS can be dopaminergic, non-dopaminergic, of genetic origin or drug induced.
- Clinical assessment of NMS should include the NMS Questionnaire (completed by patients) for screening, as recommended by the International Parkinson and Movement Disorders Society and other international societies.
- The total number of NMS in a patient with PD constitutes the NMS burden, which can be graded using validated cut-off scores on the NMS Questionnaire and Scale and can be used as an outcome measure in clinical trials.
- Despite NMS burden having a major effect on the quality of life of patients and carers, a large European study showed that NMS are often ignored in the clinic.
- The syndromic nature of PD is underpinned by non-motor subtypes which are likely to be related to specific dysfunction of cholinergic, noradrenergic, serotonergic pathways in the brain, not just the dopaminergic pathways.
- NMS can be treated by dopaminergic and non-dopaminergic strategies, but further robust studies supported by evidence from animal models are required.
- The future of modern treatment of PD needs to be supported by the delivery of personalised medicine.

Non-motor symptoms (NMS) of Parkinson disease (PD) were recognised by James Parkinson, a London-based physician in his 1817 essay on the condition he called "the shaking palsy" or "paralysis agitans".[1] He described a complex condition with tremor, gait abnormalities and stooped posture intermixed with NMS such as sleep dysfunction, delirium, dementia and dysautonomia. However, NMS remained under-recognised and poorly researched until the introduction of comprehensive tools such as the NMS Questionnaire (https://www.pdnmg.com/imagelib/pdf/nms-quest.pdf) and NMS Scale (https://www.pdnmg.com/imagelib/pdf/nms-scale08.pdf) in the early 2000s, and the recognition of PD as a condition of many origins, termed the Parkinson complex in 2006 and subsequently classified as a syndrome in 2017.[2-4] The assessment tools have helped to assess NMS holistically and to outline the effect of their burden on quality of life in PD.[5,6] NMS assessment in the outpatient clinic is now considered to be good clinical practice in many countries. Recent attempts to redefine PD have viewed it as a complex combination of motor and non-motor disorders, with a natural history that includes a prodromal phase dominated by a range of NMS. NMS-driven biomarkers may define prodromal PD and enable the identification of patients at risk of developing motor PD and the development of new neuroprotective therapies. Validated burden grading of NMS is also being increasingly used as an outcome measure in clinical trials.[7,8] Finally, the complex multi-neurotransmitter dysfunction of PD may underpin recently described non-motor subtypes.[4] Recognition of such subtypes may to lead to the emergence of personalised and precision medicine in the management of PD.[9]

This narrative review is based on a PubMed review of original and review articles from 1999 to 2017 as well as specialist society publications and relevant guidelines to formulate an evidence-based overview of the topics, as applied to clinical practice.

Non-motor symptoms in Parkinson disease

PD is the second most common neurodegenerative disorder in the world, with a global prevalence of about 200 per 100 000 individuals.[10] About one person is diagnosed every hour, one in 50 people over 80 years of age are likely to be diagnosed with PD, and about 10% of those diagnosed are below 40 years of age.[10] The number of people with PD is rising worldwide because of increasing life expectancy, and the number of diagnoses is expected to double by 2040. PD is now recognised to be as much a non-motor disorder as a motor disorder, with a complex range of NMS present in the prodromal stage as well as in the various motor disorder stages until the final palliative stage[11,12] (Box 1).

Prodromal non-motor Parkinson disease

The prodromal period of PD is now well established (Box 1). This phase is recognised by a range of NMS which include hyposmia, rapid eye movement sleep behaviour disorder (RBD) and other NMS shown in Box 2. Several cohort studies are in progress to establish how best to determine this prodromal period, which may last up to 10 years. The International Parkinson and Movement Disorder Society (MDS) has also attempted to define the prodromal period based on several NMS (eg, RBD, hyposmia, constipation, excessive daytime constipation), as well as some motor features (eg, abnormal quantitative motor testing) and other factors (eg, age, occupational exposure to solvents or pesticides, smoking, family history), and then calculate a likelihood ratio for later development of manifest PD.[13] Identification of the prodromal period is of crucial importance to enable early initiation of neuroprotective therapies at a stage when molecular degeneration begins rather than waiting until motor symptoms commence. Mutations in glucocerebrocidase or leucine-rich protein kinase genes have been implicated to mark an even earlier (pre-prodromal) stage of PD when there are no symptoms but susceptibility to PD exists (Box 1). Imaging using positron emission tomography, transcranial ultrasound and cardiac meta-iodobenzylguanidine (MIBG) scans have all been suggested as possible biomarkers in the prodromal period of PD. More recently, the role of skin biopsy as an RBD biomarker has been proposed, and cardiac MIBG scanning is now included as a supportive criterion for the clinical diagnosis of PD.[11,13,14]

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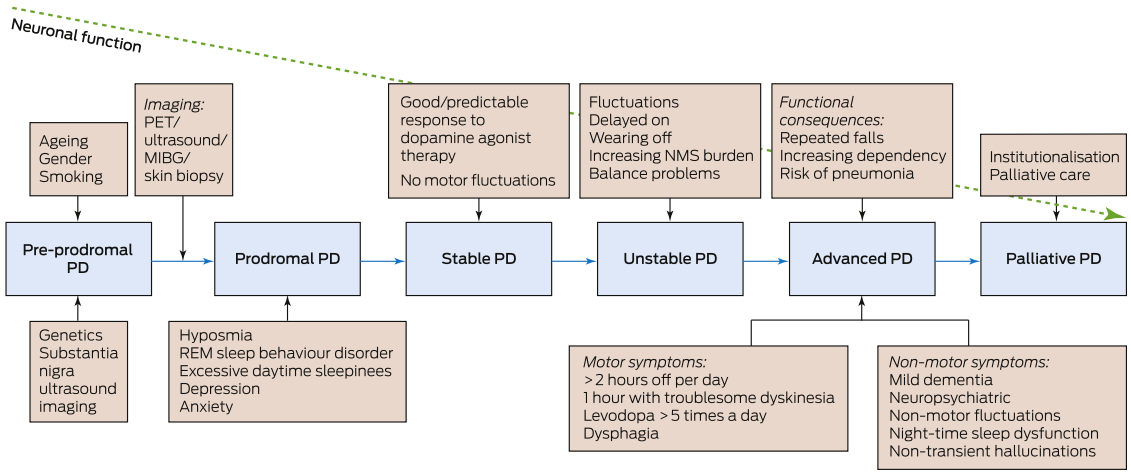
1 Natural history pattern of Parkinson disease (PD)



MIBG = meta-iodobenzylguanidine. NMS = non-motor symptoms. PET = positron emission tomography. REM = rapid eye movement. Note that the neuronal loss in PD is unlikely to follow a linear pattern (as suggested in the figure) and the relevant dotted line is a schematic representation. Imaging using transcranial ultrasound, PET and MIBG scans may be useful as markers in the prodromal period and possibly the pre-prodromal period. Skin biopsy may also be useful in patients with REM sleep behaviour disorder. Reproduced with permission from Titova et al.[11] ◆

The burden of non-motor symptoms

NMS has been studied using validated tools and cluster analysis in untreated de novo PD, early and advanced treated PD and multi-racial cohorts.[15] The range of different NMS ascertained from these studies using the NMS Questionnaire is shown in Box 3. From a global perspective, the average number of NMS per patient varies from 4 to 19 compared with controls where the scores range from 2 to 12.[15] Urinary dysfunction appears to be one of the most commonly reported NMS across several studies, followed by constipation, memory problems, anxiety and depression, fatigue and insomnia. Urinary dysfunction appears to be present throughout the spectrum of PD, being a particular challenge in the advanced palliative stage.

2 Prodromal non-motor symptoms and potential risk of development of motor Parkinson disease (PD)

Non-motor symptom	PD risk
REM sleep behaviour disorder	80% progression to α-synucleinopathy in approximately 10–12 years
REM sleep behaviour events	Polysomnography evidence of developing REM sleep behaviour disorder
Late-onset hyposmia/ anosmia	Progression to motor PD
Episodic major depression	Prodromal PD feature
Constipation	Higher risk of developing PD
Excessive daytime somnolence	Higher risk of developing PD
Fatigue	Higher risk of developing PD
Abnormal colour vision/ visual perception	Higher risk of developing PD
Erectile dysfunction	Higher risk of developing PD
Pain (often unilateral)	Pain often evident on side first affected at motor PD diagnosis
Cognitive impairment	Recent evidence of prodromal feature from PPMI cohort studies

PPMI = Parkinson Progression Marker Initiative. REM = rapid eye movement. ◆

It is now recognised that rather than considering the effect of a single NMS, it is the total number of NMS present in a patient — the NMS burden — that determines quality of life.[16,17] Globally, the rising number of people diagnosed with PD has a direct

3 Frequency of occurrence of a range of non-motor symptoms (NMS)*[15]

Non-motor symptoms	Mean	Range
Cognitive		
Memory	46%	38–63%
Concentration	39%	30–50%
Depression		
Sadness	43%	23–56%
Anxiety	43%	31–56%
Sleep		
Excessive daytime sleepiness	31%	21–37%
Insomnia	41%	18–53%
REM sleep behaviour disorder	34%	30–39%
Restless legs syndrome	36%	28–41%
Fatigue	42%	31–58%
Pain	31%	18–46%
Gastrointestinal		
Swallowing	25%	16–30%
Constipation	47%	28–72%
Urinary		
Urgency	53%	35–61%
Nocturia	54%	26–67%
NMS Questionnaire (global comparison)		
Parkinson disease patients	8	4–19
Healthy controls	4	2–12

REM = rapid eye movement. * Based on international cohort studies using the Non-motor Symptoms Questionnaire. Data for NMS Questionnaire (global comparison) are number of symptoms. ◆

consequential effect on the NMS burden, as NMS occur in virtually every patient with PD.[5,8,18] The NMS burden has a direct inverse relationship with quality of life, and the frequent occurrence of NMS has led to attempts to revise our current understanding of PD (Appendix 1). Using multiple linear regression analysis, Martinez-Martin and colleagues showed that the correlation of quality-of-life measures in PD was stronger with NMS total score determined by the NMS Scale compared with motor symptoms and complications.[6] International validation studies of the NMS Scale showed a highly significant inverse association with worsening quality of life and increasing NMS burden.[7,19] Similar data have also been found with the NMS Questionnaire.[8] In the late and palliative stage of PD, the impact of NMS is of great importance and contributes to hospitalisation and institutionalisation with high cost to society.[20,21] A large scale naturalistic Italian study of over 1000 patients also confirmed that quality of life was significantly worse in those with NMS compared with those without NMS.[17]

Classification of non-motor symptoms

NMS have non-dopaminergic and dopaminergic origins and vary widely in their nature, range and presentation.[5] It is important not to regard all NMS together as a single entity, and sub-classification of NMS helps develop and deliver true personalised medicine strategies for PD. Classification of NMS based on source of origin has been attempted and is shown in Box 4.[16,17]

4 A modern classification of non-motor symptoms (NMS) in Parkinson disease[15,16]

Dopaminergic or partial dopaminergic origin

- depression
- apathy
- early cognitive dysfunction
- wearing-off related, and aspects of central pain
- impaired colour vision
- hallucinations
- sensory, cognitive and autonomic symptoms of non-motor function
- restless legs syndrome

Non-dopaminergic origin (some dopaminergic influence is possible)

- anxiety
- dysautonomia
- hyposmia
- dementia
- fatigue
- sleep dysfunction (rapid eye movement sleep behaviour disorder, excessive daytime somnolence, insomnia)

Drug or concurrent illness (comorbidity)-induced (addition or withdrawal)

- hallucinations, other psychosis, delirium, delusion
- impulse control disorders
- dopamine agonist withdrawal syndrome
- non-motor fluctuations
- Parkinson hyperpyrexia syndrome

Genetically determined

- Mild cognitive impairment or dementia in glucocerebocidase mutation cases
- Sleep dysfunction in *LRRK2* mutation cases ◆

Neuropathology and animal models

A range of pathophysiological mechanisms operates to start and continue the neurodegenerative process of PD (Box 5).[4] Dysfunctions in the dopamine pathways in the brain and periphery are a major problem, but other major neurotransmitters such as acetylcholine, noradrenaline and serotonin are also involved.[4] Sometimes, the involvement of the non-dopaminergic pathways may be greater than dopaminergic involvement, supporting the concept of cholinergic, serotonergic and noradrenergic subtypes of PD.[2-4,16] Braak and colleagues[22,23] proposed six pathways of propagation of the pathological process in PD, commencing in the medulla and moving upwards. The proposal is based on Lewy body deposition in the brain. Stage one is associated with involvement of the olfactory bulb, anterior olfactory nucleus and the lower medulla. Stage 2 involves the lower brainstem containing non-dopaminergic nuclei such as the median raphe (serotonin) and locus coeruleus (noradrenaline) among many others. Neurodegeneration in these areas correlates clinically with late-onset hyposmia as well as RBD, which is now recognised as one of the key prodromal clinical biomarkers for the development of dementia as well as synucleinopathy, with over 80% risk of phenoconverting at 10 years.[24] Hyposmia is included as a supportive criterion for diagnosis of PD.[13] Stages 3 to 6 chart the progression of the pathological process of PD from the substantia nigra to the subcortical regions such as the basal ganglia and then the cortical area of the brain, the latter underpinning cognitive decline in advanced stages of PD.

The proportion of patients who go through all the pathological stages, and the rate of progress through these stages, is unclear. The progression pattern of PD varies and some patients may be reasonably active and independent even 20 years after the motor diagnosis of PD.[25] Controversies surrounding the concept of advanced PD have recently been reviewed by Titova and colleagues.[26] Broadly, however, most patients progress to advanced palliative stage by about 15 years after the onset of motor PD (with a variable length of prodromal period). Some initial clinical

5 Pathophysiological processes likely to be involved in the pathogenesis of Parkinson disease (PD)[4]

- Genetic and epigenetic mechanisms
  - *LRRK2*, *GBA* mutations
  - Ethnic susceptibility to PD
  - Ashkenazi Jewish population
  - Inuit populations
  - Susceptibility to organic toxins (insecticides)
  - Environment–gene interaction (higher risk in agricultural communities, lower in smokers)
- Abnormalities in α-synuclein
  - Misfolding, oligomers, altered proteostasis, neurotoxicity
  - Synaptic dysfunction
  - Ageing brain susceptibility
  - Gut–brain axis-driven prion-like intra-axonal transport
  - Altered intestinal microbiota
- Central and extra-cerebral neuroinflammation (trigger misfolding of α-synuclein)
- Amyloid and Tau deposition (older PD and PD dementia)
- Mitochondrial dysfunction/reduced complex 1 activity (cell damage and death)
- Altered gut microbiota (reduced mucin and inflammatory spread to brain [gut–brain axis])
- Neurotransmitter dysfunction (altered signalling in brain) ◆

biomarkers may suggest relatively rapid progression of PD and include patients with RBD and dysautonomia at the onset of the illness or those with early gait-related problems.

The peripheral nervous system, spinal cord as well as multiple viscera and skin are involved in PD and may express a range of NMS (Appendix 2).[27,28] Neuropathology including α-synuclein deposition is seen in peripheral organs such as the heart, gut, submandibular glands and skin, indicating the widespread involvement of the peripheral nervous system in PD. The spread of α-synuclein deposition and consequent clinical non-motor effects have recently been reviewed by Jellinger.[27] Peripheral tissue biopsy may emerge as a feasible biomarker for some specific NMS in PD, and skin biopsy has been proposed as a potential biomarker in RBD.[14]

To properly understand NMS in PD, robust animal models that express progressive neurodegeneration with Lewy body formation are required. Currently, there are no such models. Experimental animal models can assist in understanding the pathogenesis of the range of NMS, which in turn can help with potential approaches to their treatment. Knowledge of current developments in relation to attempts at producing animal models is therefore important to understand the pathophysiology of NMS in PD as well as to develop new treatments, currently a key unmet need. A list of potential animal models with a variety of NMS is shown in Appendix 3.[29]

Non-motor symptom clinical measurement

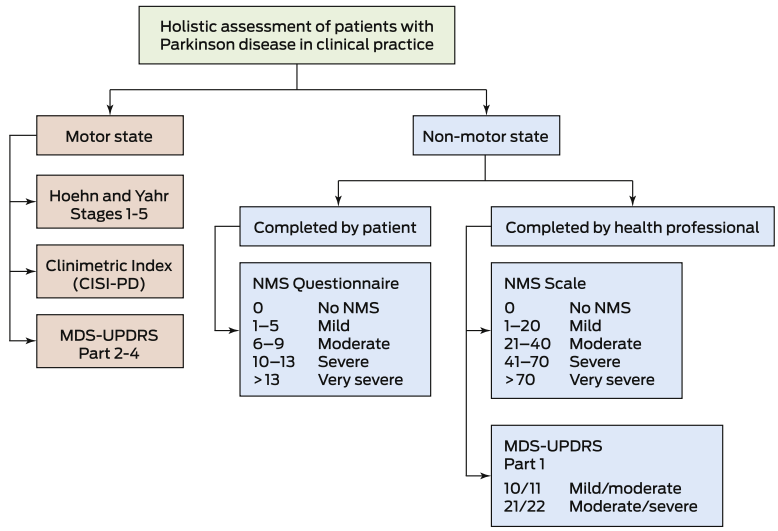
Holistic and widely validated tools such as the NMS Questionnaire[30] and Scale[31] are available and are recommended by the MDS. The NMS Questionnaire is a self-reporting tool completed by patients and is instrumental as a flagging tool in the clinic that is useful for epidemiological studies.

Holistic measurements of NMS are now supported by validation of the grading of burden using the NMS Questionnaire[8] and Scale[7,32] (Appendix 1). To ensure that the NMS status of patients with PD is assessed in parallel with their motor symptoms, recent reviews have recommended that the NMS assessment tools be used in combination with motor assessment (Hoehn and Yahr staging).[33] A key recommendation would be to combine Hoehn and Yahr staging with the NMS Questionnaire grading for patients, performed at least once a year. A suggested paradigm for use in the clinic is shown in Box 6. Additional tools include the Unified PD Rating Scale, the Clinical Impression of Severity Index for PD, as well as a wearing-off questionnaire to address non-motor fluctuations. The Unified PD Rating Scale is the most widely used clinical scale for PD worldwide, and the Clinical Impression of Severity Index for PD has been specifically validated. Combined use for gradation strategies incorporating motor and non-motor measurements have been reviewed recently.[34,35]

Non-motor fluctuations

Non-motor fluctuations almost always accompany motor fluctuations and have been classified into autonomic, sensory and cognitive subtypes. Storch and colleagues[36] have described NMS that are present exclusively during off periods, while others are present during on periods and worsen during off periods. Clinically, non-motor fluctuations usually manifest with anxiety, pain, drenching sweats, clouding of mind, fatigue and depression. However, some NMS such as euphoria may occur exclusively during on periods.

6 A proposed algorithm for a combined motor and non-motor assessment of non-motor symptoms (NMS) in the clinic to determine a patient's non-motor status*

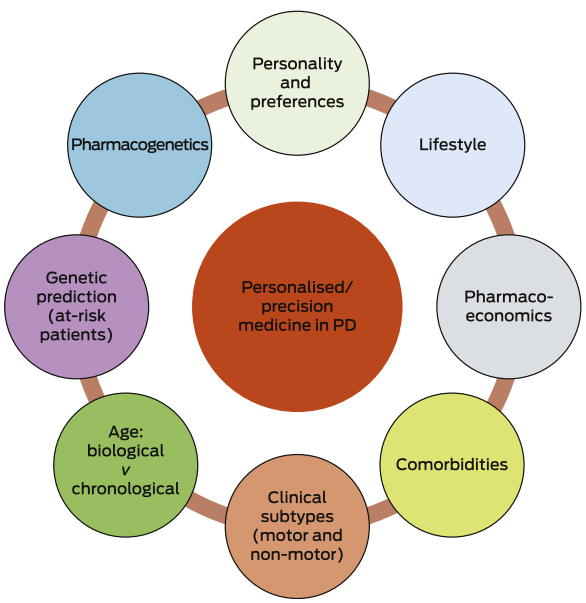


CISI-PD = Clinical Impression of Severity Index for Parkinson Disease. MDS = Movement Disorders Society. UPDRS = Unified Parkinson Disease Rating Scale. *All cut-off values quoted are validated from clinical studies. Rapid assessment in the clinic could be performed using Hoehn and Yahr motor staging and the self-completed NMS Questionnaire and subsequent burden grading. Adapted with permission from Katunina and Titova.[15] ◆

Non-motor subtyping

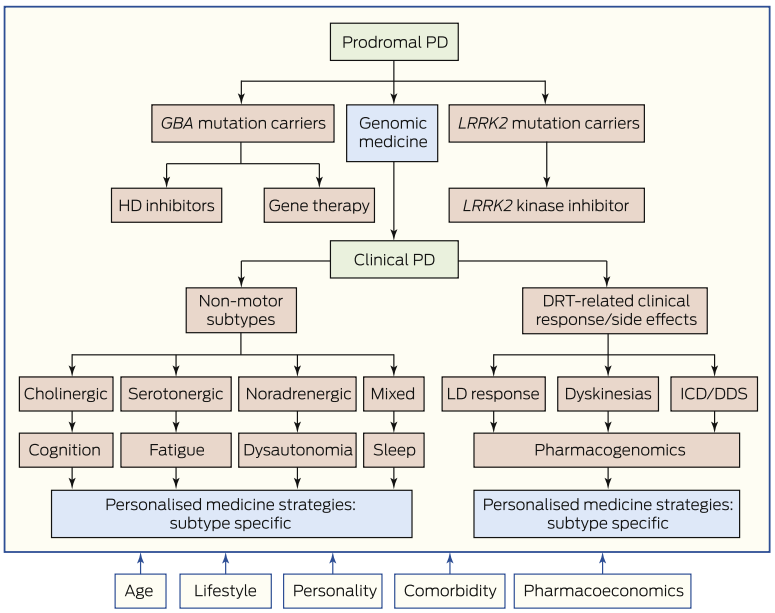
Non-motor subtypes have been described using multidimensional cluster analysis studies in untreated patients and those with early PD. These report discrete clusters of patients expressing specific NMS.[37,38] Clinical characterisation of these clusters

7 Factors that may drive or enable pathways for personalised and precision medicine in Parkinson disease (PD)



Reproduced with permission from Titova and Chaudhuri.[9] ◆

8 A summary of the various components and strategies proposed to establish a comprehensive and holistic personalised medicine strategy for Parkinson disease (PD)



DDS = dopamine dysregulation syndrome. DRT = dopamine replacement therapy. *GBA* = glucocerebrocidase. HD = histone deacetylase. ICD = impulse control disorder. LD = levodopa response. *LRRK2* = leucine-rich repeat kinase 2. PD = Parkinson disease. Reproduced with permission from Titova and Chaudhuri.[9] ◆

identifies specific NMS dominant phenotypes: Park cognition, Park apathy, Park depression/anxiety, Park sleep, Park pain, Park fatigue and Park autonomic.[34,39-41] Further cohort studies are required to define the specific clinical characteristics of these subtypes as well as biomarkers and natural history. A more relevant neurotransmitter dysfunction-based non-motor classification has been proposed by Titova and colleagues,[4] supported by imaging and other biomarker studies. This classification forms the basis of the concept that PD may well be a syndromic condition associated with a range of complex disorders underpinned by specific neurotransmitter deficits. The cholinergic syndrome has been well characterised clinically[42] and in de novo PD,[43] and cholinergic imaging of the brain and the gut supports this concept.[44-47] Such patients may have a higher risk of progression to dementia.[46] Noradrenergic syndrome is also well characterised and patients express dominantly autonomic dysfunction.[48] Patients with the serotonergic subtype, however, suffer from severe fatigue and may develop levodopa-induced dyskinesias.[49] These neurotransmitter-driven syndromic presentations[4] underpin the modern concept of personalised medicine for PD.[9]

Treatment of non-motor symptoms

Management of NMS in PD presents one of the key challenges in clinical practice. An evidence-based medicine review by the MDS[50] and a recent review by Schrag and colleagues[51] highlight key unmet needs. The role of non-pharmacological therapies, such as various forms of exercise (yoga, tai chi), cognitive behaviour therapy and transcranial magnetic stimulation, is being explored, particularly for depression, anxiety and cognitive problems. Increasing attention has focused on probiotic treatment for abnormal gut flora in PD. However, for many NMS, such as fatigue, sexual dysfunction, apathy, and urinary dysfunction, there is insufficient evidence of treatment.

Personalised medicine

Personalised medicine is the modern way of delivering an individualised holistic PD treatment strategy.[9,52] Personalised medicine thus encompasses several strands of treatment known as the enablers. From a pharmacological point of view, it should involve dopaminergic and non-dopaminergic strategies. In addition, there are sub-strategies involving precision and tailored medicine to suit the needs and requirements of individual patients. Precision medicine is relevant for patients who may be at risk of developing the clinical syndrome of PD as identified by specific gene mutations. Precision medicine in this scenario attempts to be preventive. Tailored medicine works with the single multi-factorial complex nature of PD to manage symptoms and develop subtype-specific strategies. Personalised medicine is now being applied to other conditions such as stroke, mental health, oncology as well as diabetes. In PD, neurotransmitter subtype-based individualised treatment can be considered. Patients with the cholinergic subtype could be treated by a combination of dopaminergic and cholinesterase inhibition therapy while also undertaking active counselling regarding lifestyle, job, exercise and freezing of gait.[46] Patients with the noradrenergic subtype would require a focus on noradrenergic treatment for dysautonomia, whereas patients with serotonergic subtype fatigue could be managed by serotonin active drugs. However, robust clinical trials for such strategies are not available and trials are in progress.

Several factors influence the delivery of personalised medicine in PD (Box 7). A summary of pathways which may help deliver personalised medicine for PD is shown in Box 8. These range from genomic medicine to subtype/syndrome and symptom specific care.

Conclusion

PD is a motor and non-motor disorder from the onset of the condition. Indeed, prodromal PD is largely non-motor. Key advances include the development of validated tools for holistic measurement of NMS, grading of the NMS burden, and a focus on multi-modal biomarkers to define non-motor PD subtypes. The latter is likely to lead to better management of NMS in PD. Future strategies should focus on developing robust animal models for specific NMS to provide a better understanding of the pathophysiology, which will enable development of personalised treatment strategies. The under-recognition of the burden of NMS and its effects can be remedied by better education of clinicians and caregivers. Only then will NMS cease to be the hidden painful face of PD.

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